CLAIMS

We Claim:

1. An active ester compound that is a 5, 6 or 7 membered heterocyclic ring comprising a ring nitrogen atom that is N-alkylated with a substituted or unsubstituted acetic acid moiety to which the alcohol moiety of the active ester is linked through the carbonyl carbon of the N-alkyl acetic acid moiety, wherein the compound is isotopically enriched with one or more heavy atom isotopes.

2. The compound of claim 1, wherein the compound is isotopically enriched with three or more heavy atom isotopes.

3. The compound of claim 1, wherein the heterocyclic ring is substituted with one or more substituents.

4. The compound of claim 3, wherein the one or more substituents are alkyl, alkoxy or aryl groups.

5. The compound of claim 4, wherein the one or more substituents are protected or unprotected amine groups, hydroxyl groups or thiol groups.

6. The compound of claim 1, wherein the heterocyclic ring is aliphatic.

7. The compound of claim 1, wherein the heterocyclic ring is aromatic.

8. The compound of claim 1, wherein the heterocyclic ring comprises one or more additional nitrogen, oxygen or sulfur atoms.

9. The compound of claim 1, wherein active ester is an N-hydroxysuccinimide ester.

10. The compound of claim 1, wherein the compound is a salt.

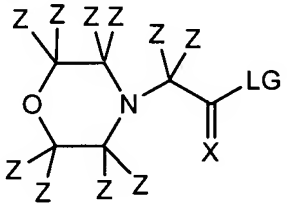
11. The compound of claim 1, wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt.

12. The compound of claim 1, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.

13. The compound of claim 1, wherein each incorporated heavy atom isotope is present in at least 93 percent isotopic purity.

14. The compound of claim 1, wherein each incorporated heavy atom isotope is present in at least 96 percent isotopic purity.

15. An N-substituted morpholine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester;

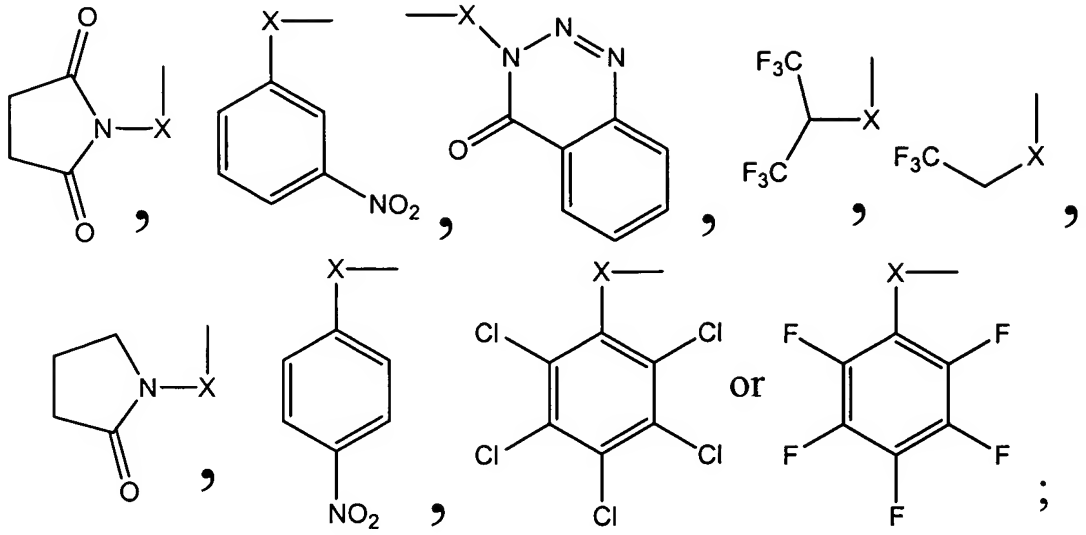
X is O or S;

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms; and

wherein the N-substituted morpholine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

16. The compound of claim 15, wherein the N-substituted morpholine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

17. The compound of claim 15, wherein LG is:



and wherein X is O or S.

18. The compound of claim 15, wherein LG is N-hydroxysuccinimide.

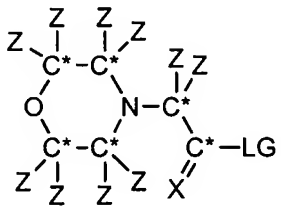
19. The compound of claim 15, wherein each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

20. The compound of claim 15, wherein each Z is independently hydrogen, methyl or methoxy.

21. The compound of claim 15, wherein X is ^{16}O or ^{18}O.

22. The compound of claim 15, wherein the nitrogen atom of the morpholine ring is ^{14}N or ^{15}N.

23. The compound of claim 15, of the formula:



wherein;

each C* is independently ^{12}C or ^{13}C;

LG is the leaving group of an active ester;

X is O or S; and

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

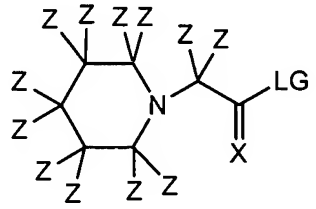
24. The compound of claim 15, wherein the compound is a mono-TFA salt or a mono-HCl salt.

25. The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.

26. The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.

27. The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.

28. An N-substituted piperidine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester;

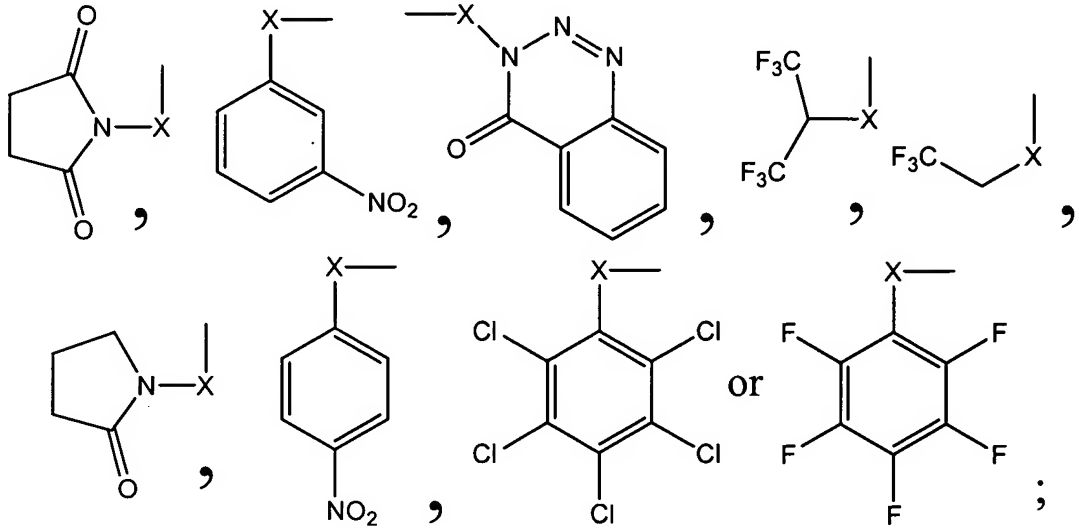
X is O or S;

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms; and

wherein the N-substituted piperidine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

29. The compound of claim 28, wherein the N-substituted piperidine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

30. The compound of claim 28, wherein LG is:



and wherein X is O or S.

31. The compound of claim 28, wherein LG is N-hydroxysuccinimide.

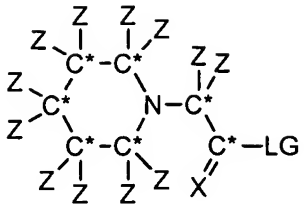
32. The compound of claim 28, wherein each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

33. The compound of claim 28, wherein each Z is independently hydrogen, methyl or methoxy.

34. The compound of claim 28, wherein X is ^{16}O or ^{18}O.

35. The compound of claim 28, wherein the nitrogen atom of the piperidine ring is ^{14}N or ^{15}N.

36. The compound of claim 28, of the formula:



wherein;

each C* is independently ^{12}C or ^{13}C;

LG is the leaving group of an active ester;

X is O or S; and

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

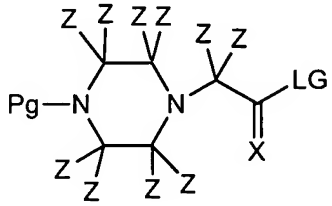
37. The compound of claim 28, wherein the compound is a mono-TFA salt or a mono-HCl salt.

38. The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.

39. The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.

40. The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.

41. An N-substituted piperazine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester;

X is O or S;

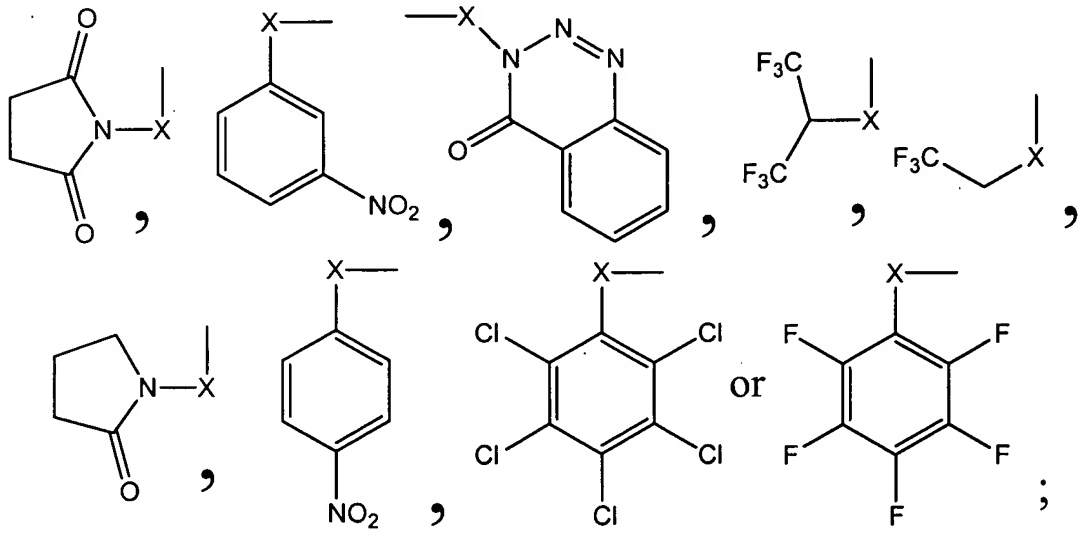
Pg is an amine-protecting group;

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms; and

wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

42. The compound of claim 41, wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes

43. The compound of claim 41, wherein LG is:



and wherein X is O or S.

44. The compound of claim 41, wherein LG is N-hydroxysuccinimide.

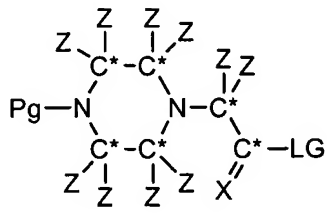
45. The compound of claim 41, wherein each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

46. The compound of claim 41, wherein each Z is independently hydrogen, methyl or methoxy.

47. The compound of claim 41, wherein X is ^{16}O or ^{18}O.

48. The compound of claim 41, wherein each nitrogen atom of the piperazine ring is ^{14}N or ^{15}N.

49. The compound of claim 41, of the formula:



wherein,

each C* is independently ^{12}C or ^{13}C;

LG is the leaving group of an active ester;

X is O or S;

Pg is an amine protecting group; and

each Z is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

50. The compound of claim 41, wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt

51. The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.

52. The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.

53. The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.

54. A kit comprising:

a) a set of two or more reagents suitable for the labeling of analytes, each reagent of the set comprising the formula:

RP-X-LK-Y-RG

or a salt thereof wherein;

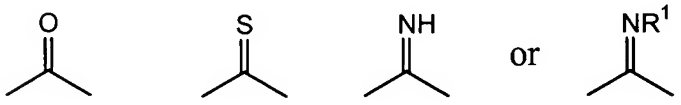
i) RG is a reactive group that is an electrophile and that is capable of reacting with one or more of the reactive analytes of the sample;

ii) RP is a reporter moiety that comprises a fixed charge or that is ionizable, wherein the gross mass of each reporter is different for each reagent of the set;

iii) LK is a linker moiety that links the reactive group and the reporter group, wherein:

a) the mass of the linker compensates for the difference in gross mass between the reporters for the different labeling reagents of the set such that the aggregate gross mass of the reporter and linker combination is the same for each reagent of the set; and

b) the linker comprises at least one heavy atom isotope and has the formula:



wherein R^1 is the same or different and is an alkyl group comprising one to eight carbon atoms which may optionally contain a heteroatom or a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen, deuterium and/or fluorine atoms;

iv) X is a bond between an atom of the reporter and an atom of the linker;

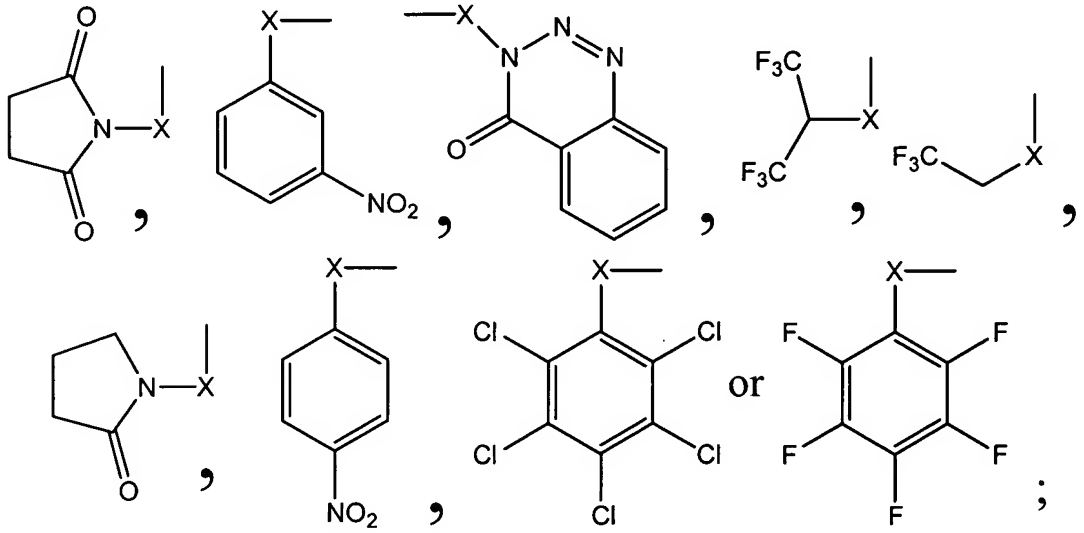
v) Y is a bond between an atom of the linker and an atom of the reactive group, wherein, once the labeling reagent is reacted with the reactive analyte, bond Y links the linker to the analyte; and

b) one or more reagents, containers, enzymes, buffers or instructions.

55. The kit of claim 54, wherein the kit comprises a proteolytic enzyme.

56. The kit of claim 54, wherein the reactive group of each reagent of the set is an active ester.

57. The kit of claim 56, wherein the alcohol moiety of the active ester is a group of the formula:



wherein X is O or S.

58. The kit of claim 56, wherein the active ester is an N-hydroxysuccinimide ester.

59. The kit of claim 54, wherein the reporter is a substituted or unsubstituted morpholine, piperidine or piperazine.

60. The kit of claim 54, wherein the reporter comprises a carboxylic acid, sulfonic acid or phosphoric acid group.

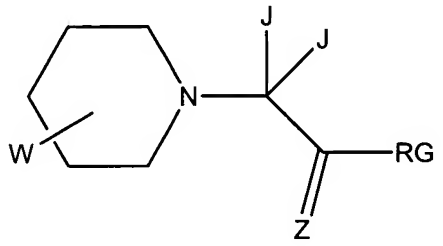
61. The kit of claim 54, wherein the linker is a carbonyl or thiocarbonyl group.

62. The kit of claim 54, wherein each reagent of the set is independently linked to a solid support through a cleavable linker.

63. The kit of claim 54, wherein all reagents of the set are isomeric.

64. The kit of claim 54, wherein all reagents of the set are isobaric.

65. The kit of claim 64, wherein all reagents of the set comprise the formula:



wherein;

a) RG is a reactive group that is an electrophile;

b) Z is O, S, NH or NR^1;

c) each J is the same or different and is selected from the group consisting of: H, deuterium (D), R^1, OR^1, SR^1, NHR^1, $N(R^1)_2$, fluorine, chlorine, bromine and iodine;

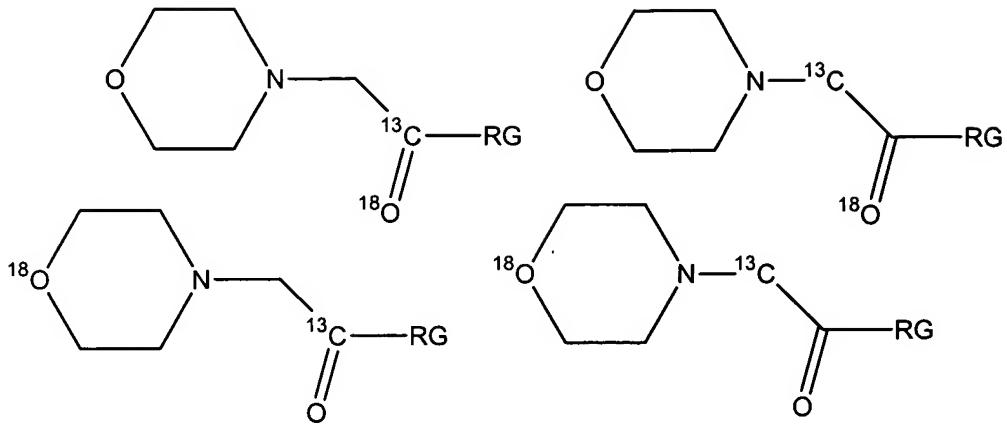
d) W is an atom or group that is located ortho, meta or para to the ring nitrogen and is selected from the group consisting of: NH, N-R^2, P-R^2, O or S; and

e) each carbon of the heterocyclic ring has the formula CJ_2;

f) each R^1 is the same or different and is an alkyl group comprising one to eight carbon atoms which may optionally contain a heteroatom or a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen deuterium and/or fluorine atoms; and

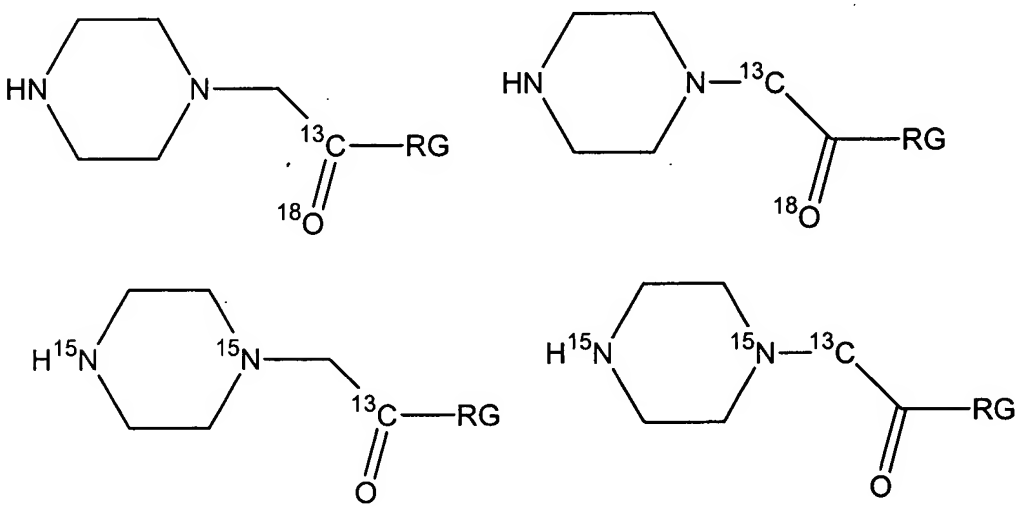
g) R^2 is an amino alkyl, hydroxy alkyl, thio alkyl group or a cleavable linker that cleavably links the reagent to a solid support wherein the amino alkyl, hydroxy alkyl or thio alkyl group comprises one to eight carbon atoms, which may optionally contain a heteroatom or a substituted or unsubstituted aryl group, and wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen, deuterium and/or fluorine atoms.

66. The kit of claim 65, wherein the set comprises one or more of the following four reagents:



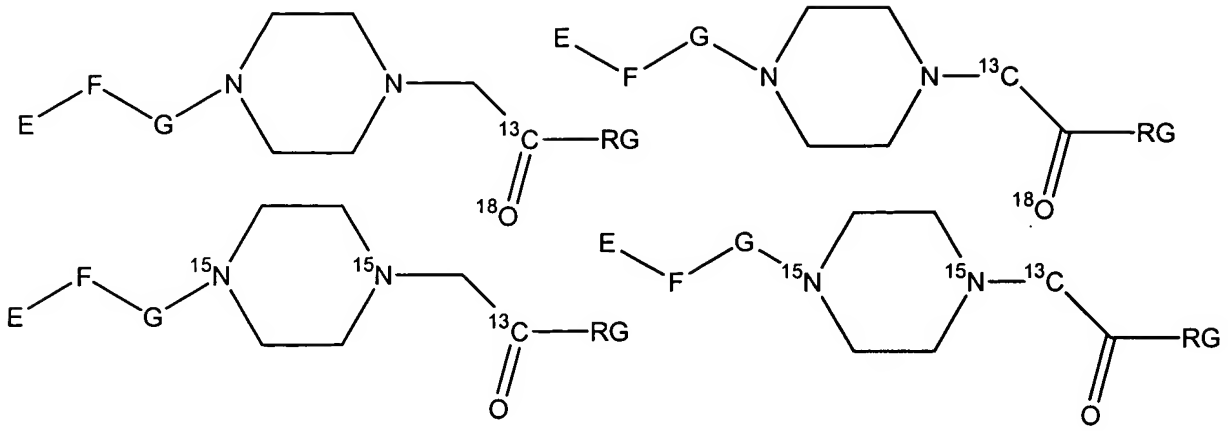
wherein RG is the reactive group.

67. The kit of claim 65, wherein the set comprises one or more of the following four reagents:



wherein RG is the reactive group.

68. The kit of claim 65, wherein the set comprises one or more of the following four support bound reagents:



wherein:

a) RG is the reactive group;

b) E is a solid support;

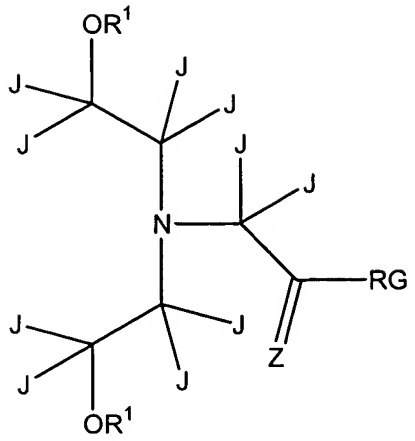
c) F is a cleavable linker linked to the solid support;

d) G is an amino alkyl, hydroxy alkyl or thio alkyl group, cleavably linked to the cleavable linker wherein the amino alkyl, hydroxy alkyl or thio alkyl group comprises one to eight carbon atoms, which may optionally contain a heteroatom or a substituted or unsubstituted aryl group, and wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen, deuterium and/or fluorine atoms;

e) each carbon of the heterocyclic ring has the formula CJ_2; and wherein each J is the same or different and is selected from the group consisting of: H, deuterium (D), R^1, OR^1, SR^1, NHR^1, $N(R^1)_2$, fluorine, chlorine, bromine and iodine; and

f) each R^1 is the same or different and is an alkyl group comprising one to eight carbon atoms which may optionally contain a heteroatom or a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen, deuterium and/or fluorine atoms.

69. The kit of claim 65, wherein all reagents of the set comprise the formula:



wherein:

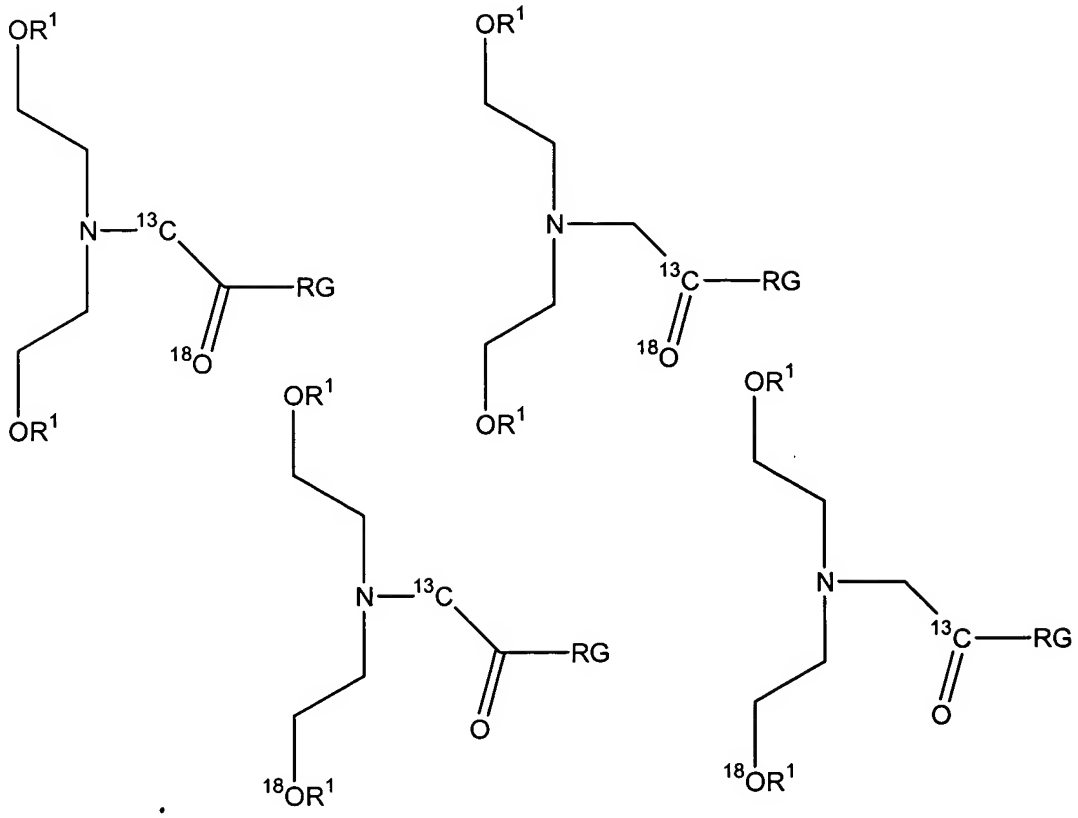
a) RG is a reactive group that is a nucleophile or electrophile;

b) Z is O, S, NH or NR^1;

c) each J is the same or different and is selected from the group consisting of: H, deuterium (D), R^1, OR^1, SR^1, NHR^1, $N(R^1)_2$, fluorine, chlorine, bromine and iodine; and

d) each R^1 is the same or different and is an alkyl group comprising one to eight carbon atoms which may optionally contain a heteroatom or a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen deuterium and/or fluorine atoms.

70. The kit of claim 65, wherein the set comprises one or more of the following four reagents:



wherein RG is the reactive group.